

<110> INSERM

<120> IL-15 binding site for IL15-Ralpha, and specific agonists/antagonists deriving therefrom

<130> FP/CC - PCT IL-15 muteins INSERM

<150> ep04290542.2

<151> 2004-02-27

<160> 85

<170> PatentIn version 3.2

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PCT IL15 muteins.ST25.txt

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Val Phe Ile Leu Gly Cys Phe Ser Ala Gly Leu Pro Lys Thr Glu Ala
35 40 45
Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
50 55 60
Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
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Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
85 90 95

PCT IL15 muteins.ST25.txt

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
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Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
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PCT IL15 muteins.ST25.txt

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35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Lys Glu Leu Gln
35 40 45
Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60
Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80
Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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35 40 45
Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60
Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
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35 40 45

Val Ile Asp Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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35 40 45
Val Ile Lys Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60
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65 70 75 80
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 20 25 30

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 35 40 45

Val Ile Arg Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
 50 55 60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
 65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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 35 40 45

Val Ile Ser Asp Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
 50 55 60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
 65 70 75 80

PCT IL15 muteins.ST25.txt

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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35 40 45

Val Ile Ser Glu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
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Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
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Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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35 40 45

Val Ile Ser Lys Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
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Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
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20 25 30

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35 40 45

Val Ile Ser Arg Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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 35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Lys
 50 55 60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
 65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
 85 90 95

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Thr Ser

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 20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
 35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Arg
 Page 16

50

55

60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
 65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
 85 90 95

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 20 25 30

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 35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
 50 55 60

Asp Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
 65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
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Glu Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
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Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
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Lys Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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PCT IL15 muteins.ST25.txt

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Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Arg Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser

<210> 47
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> IL15 mutant

<400> 47

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20 25 30

PCT IL15 muteins.ST25.txt

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Asp Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser

<210> 48
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> IL15 mutant

<400> 48

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Glu Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser

<210> 49

PCT IL15 muteins.ST25.txt

<211> 114
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 <213> Artificial Sequence

<220>
 <223> IL15 mutant

<400> 49

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
 1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
 20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
 35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
 50 55 60

Asn Leu Ile Lys Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
 65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
 85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
 100 105 110

Thr Ser

<210> 50
 <211> 114
 <212> PRT
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<220>
 <223> IL15 mutant

<400> 50

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
 1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
 20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
 35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
 50 55 60

Asn Leu Ile Arg Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val

65 70 PCT IL15 muteins.ST25.txt 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser

<220>
<223> IL-2Rbeta sense primer

<210> 52
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> IL-2Rbeta anti-sense primer

<210>	53
<211>	20
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<223>	IL-2Ralpha sense primer

<210>	54
<211>	20
<212>	DNA
<213>	Artificial Sequence
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<210>	55
<211>	28
<212>	DNA
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PCT IL15 muteins.ST25.txt

<220>
 <223> IL-2 sense primer
 <400> 55
 aactgcaggc acctacttca agttctac 28

<210> 56
 <211> 28
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> IL-2 anti-sense primer
 <400> 56
 tcccccggt caagtcagtg ttgagatg 28

<210> 57
 <211> 27
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> IL-15Ralpha-IL-2 sense primer
 <400> 57
 gggaagctta gtccagcgt gtcctgt 27

<210> 58
 <211> 26
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> IL-15Ralpha-IL-2 anti-sense primer
 <400> 58
 aactgcagag tgggtgctgct gtggcc 26

<210> 59
 <211> 27
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> sense primer for rat prepolactin signal peptide
 <400> 59
 ggggtaccat caccatgaac agccaag 27

<210> 60
 <211> 27
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> antisense primer for rat preprolactin signal peptide
 <400> 60
 cgggatccgg tctgcacatt ttggcag 27

<210> 61

PCT IL15 muteins.ST25.txt

<211> 28
 <212> DNA
 <213> Artificial Sequence
 <220>
 <223> sense primer for mature human IL-15
 <400> 61
 cgggatccaa ctgggtgaat gtaataag 28

<210> 62
 <211> 26
 <212> DNA
 <213> Artificial Sequence
 <220>
 <223> antisense primer for mature human IL-15
 <400> 62
 ggaattctca agaagtgttg atgaac 26

<210> 63
 <211> 8
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> FLAG tag
 <400> 63
 Asp Tyr Lys Asp Asp Asp Asp Lys
 1 5

<210> 64
 <211> 30
 <212> DNA
 <213> Artificial Sequence
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 <223> FLAG tag oligo
 <400> 64
 gatcggacta caaggatgac gatgacaagc 30

<210> 65
 <211> 30
 <212> DNA
 <213> Artificial Sequence
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 <223> FLAG tag oligo
 <400> 65
 gatcgcttgt catcgatcatc cttgtagtcc 30

<210> 66
 <211> 18
 <212> DNA
 <213> Homo sapiens
 <400> 66
 gaaaatctga tcatccta 18

PCT IL15 muteins.ST25.txt

<210> 67
 <211> 6
 <212> PRT
 <213> Homo sapiens

<400> 67

Glu Asn Leu Ile Ile Leu
 1 5

<210> 68
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> IL15 mutant

<400> 68

Lys Asn Leu Ile Ile Leu
 1 5

<210> 69
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> IL15 mutant

<400> 69

Arg Asn Leu Ile Ile Leu
 1 5

<210> 70
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> IL15 mutant

<400> 70

Glu Asp Leu Ile Ile Leu
 1 5

<210> 71
 <211> 6
 <212> PRT
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<220>
 <223> IL15 mutant

<400> 71

Glu Glu Leu Ile Ile Leu
 1 5

PCT IL15 muteins.ST25.txt

<210> 72
 <211> 6
 <212> PRT
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<220>
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<400> 72

Glu Lys Leu Ile Ile Leu
 1 5

<210> 73
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> IL15 mutant

<400> 73

Glu Arg Leu Ile Ile Leu
 1 5

<210> 74
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> IL15 mutant

<400> 74

Glu Asn Leu Ile Asp Leu
 1 5

<210> 75
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> IL15 mutant

<400> 75

Glu Asn Leu Ile Glu Leu
 1 5

<210> 76
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> IL15 mutant

<400> 76

Glu Asn Leu Ile Lys Leu

1

5

<210> 77
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 77

Glu Asn Leu Ile Ile Asp
 1 5

<210> 78
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 78

Glu Asn Leu Ile Ile Glu
 1 5

<210> 79
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> IL15 mutant

<400> 79

Glu Asn Leu Ile Ile Lys
 1 5

<210> 80
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> IL15 mutant

<400> 80

Glu Asn Leu Ile Ile Arg
 1 5

<210> 81
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> IL15 mutant

<400> 81

PCT IL15 muteins.ST25.txt

Glu Asn Leu Ile Arg Leu
1 5

<210> 82
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> IL15 mutant

<400> 82

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Asp Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser

<210> 83
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> IL15 mutant

<400> 83

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

PCT IL15 muteins.ST25.txt

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Glu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser

<210> 84
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> IL15 mutant

<400> 84

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Lys Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser

<210> 85
<211> 114
<212> PRT
<213> Artificial Sequence

PCT IL15 muteins.ST25.txt

<220>

<223> IL15 mutant

<400> 85

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Arg Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser